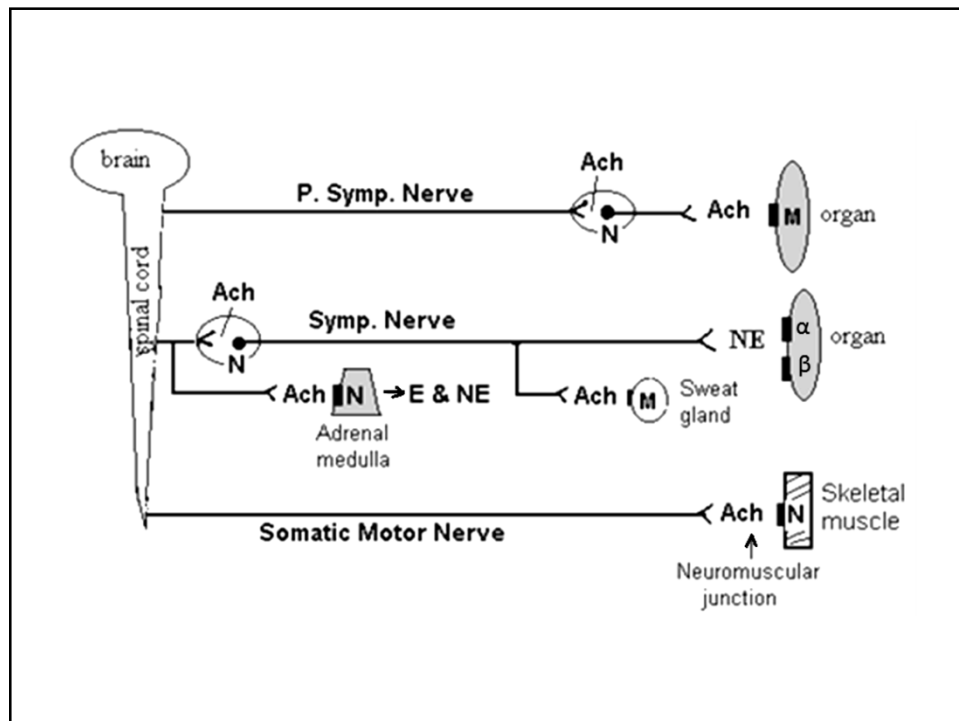


# CHOLINERGIC ANTAGONISTS

Parasympatholytics



# Cholinergic Antagonists

(cholinergic blockers, parasympatholytics or anticholinergic drugs)

- They include 3 classes:
  1. Muscarinic Antagonist.
  2. Ganglion Blockers (Nn).
  3. Neuromuscular Blockers (Nm).

## 1. Muscarinic Antagonists

- They block muscarinic receptors, causing inhibition of all parasympathetic functions.
- They block the few exceptional sympathetic neurons that are cholinergic?
- They are effective in several clinical situations unlike cholinergic agonists
- Drugs belong to this group:
  - Atropine
  - Scopolamine
  - Ipratropium

} Belladonna alkaloids

# Atropine

- A tertiary amine has a high affinity for M receptors competing with Ach.
- Atropine acts both centrally and peripherally.

## Cardiovascular effect:

### **Heart**

- At low doses: ↓HR (due to central activation of vagal nerve (CIC) or blockade of presynaptic M1 → ↑Ach release).
- At higher doses (1 mg of atropine): Blocks M2 receptors on the SA node → ↑HR

**BV:** No effect (at large dose » vasodilation of skin BV)

**BP:** No effect

## Exocrine glands:

- At low dose → ↓salivary, lachrymal, bronchial & sweat glands
- Inhibition of secretions by sweat glands can cause elevated body temp
- It produces uncomfortable dry mouth (xerostomia) & skin
- Gastric secretion is not affected (pirenzepine is specific M1 antagonist and can be used for peptic ulcer).

## Smooth Muscles:

- Bronchi: Bronchodilation, ↓ bronchial secretion (**ipratropium**)
- GIT: at large dose ↓ motility (antispasmodic effect, also scopolamine), No effect on HCL secretion (**pirenzepine**)
- Urinary Bladder: Wall relaxation & sphincter contraction. It is still occasionally used in enuresis (involuntary voiding of urine), but TCA & α-adrenergic antagonists are more preferred.

## Eye:

- Iris: **Passive mydriasis** & becomes **unresponsive to light**.
- Ciliary Muscle: Paralysis of accommodation (cycloplegia, inability to focus for near vision).
- In patient with narrow angle glaucoma, IOP may rise dangerously, so short acting antimuscarinic tropicamide or a agonist **phenylephrine** are more preferred in ophthalmic examination.

## Clinical Uses of Atropine

- Ophthalmic: Mydriatic & cycloplegic effects (disadv. of atropine ?)
- Antispasmodic agent: Atropine is used as an antispasmodic agent to relax the GI tract & bladder.
- Antidote for cholinergic agonists: Used for the treatment of overdoses of cholinesterase inhibitors such as:
  - physostigmine & organophosphate insecticides
  - Mushrooms
  - The ability of atropine to enter CNS is of particularly importance
- Antisecretory agent: To dry secretions & prevent reflex bronchoconstriction during anaesthesia
- Treatment of cholinergic crisis in myasthenia gravis.

- Tropicamide and cyclopentolate are used as ophthalmic solutions for similar conditions as atropine (mydriasis and cyclopegia).
- Their duration of action is shorter than atropine (less adverse effects)

## Scopolamine

- Like Atropine, it is a tertiary amine but has greater action on the CNS and a longer duration in comparison to those of atropine
- It is most effective anti-motion sickness drug available
- It has unusual effect of blocking short-term memory, so it an important adjunct drug in anesthetic procedure
- In contrast to atropine, scopolamine produces sedation, but at higher doses it can produce excitement instead

### **Ipratropium & Tiotropium**

- It is a quaternary derivative of atropine i.e. does not enter CNS
- Used in treatment of **asthma** and chronic obstructive pulmonary diseases (COPD) in patients who are unable to take adrenergic agonists.

### **Benztropine & Trihexphenidyl**

- Used for the treatment of parkinsonism

### **Darifenacin ,Fesoterodine & Oxybutynin**

- Atropine-like drugs that are used for overactive urinary bladder.
- Oxybutynin is used as transdermal patches (less dry mouth effect).

### **Adverse Effects of Muscarinic Antagonists**

- Dry mouth & blurred vision (sandy eyes).
- Tachycardia.
- Constipation.
- Restlessness, confusion, hallucination & delirium, which may progress to depression, collapse of the circulatory and respiratory systems and death.
- Flushing & fever.

#### **In elderly:**

- Glaucoma (may cause an attack of glaucoma in someone with a latent condition).
- Urinary retention .

Low doses of cholinesterase inhibitors such as physostigmine may be used to overcome atropine toxicity.

## 2. Ganglionic Blockers (Nn)

- They block nicotinic receptors of autonomic ganglia, (no selectivity for symph. or parasympth. ganglia) therefore they are rarely used therapeutically (experimental tools in pharmacology).
- **Two classes:**
  - Depolarizing Ganglionic Blockers:  
e.g Nicotine (only one)
  - Competitive Ganglionic Blockers:  
e.g. Mecamylamine & Trimetaphan

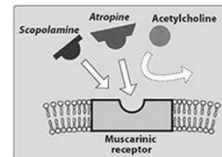
### Competitive Ganglionic Blockers

- They block both sympathetic & parasympathetic ganglia
- Produced effects are related to dominant ganglia
- Sympathetic ganglia are dominant to blood vessels & sweat glands so when blocked → ↓BP
  - (Mecamylamine & Trimetaphan may be used to produce controlled hypotension to minimize bleeding during certain kinds of surgery).
- Parasympathetic ganglia are dominant to heart, eye, GIT, urinary bladder & exocrine glands so when blocked → atropine like actions.

### 3. Neuromuscular Blockers

#### Drugs can block neuromuscular transmission by:

1. Inhibiting Ach synthesis
  - e.g. hemicholinum & triethylcholine
2. Inhibiting Ach release
  - e.g. botulinum toxins, excess  $Mg^{2+}$ , aminoglycosides antibiotics.
3. Interfering with the postsynaptic action of Ach:
  - a) Depolarizing Blocking Agents (DNMB)
    - Produce initial stimulation followed by failure of transmission
    - e.g. succinylcholine & decamethonium
  - b) Competitive (non-depolarizing) Blocking Agents (CNMB)
    - They are pure antagonists
    - e.g. curare & gallamine



#### Neuromuscular Blockers

- They are useful clinically as skeletal muscle relaxant and to facilitate intubation in surgery and so decrease the dose of anesthetic drug.

#### **Other Muscle Relaxants**

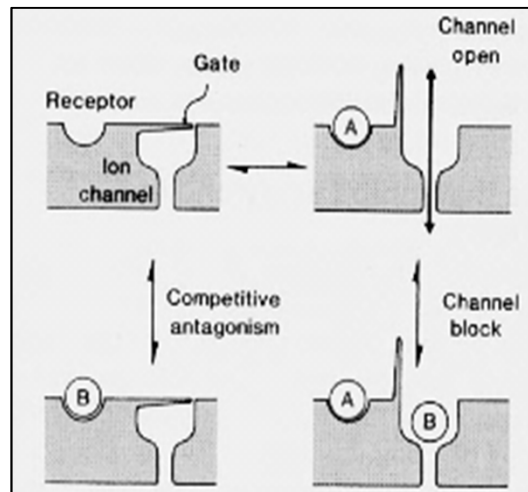
- Central muscle relaxant like **diazepam** & **baclofen** by interacting with  $\gamma$ -aminobutyric acid (GABA) receptors.
- **Dantrolene** which acts directly on muscles by interfering with the release of  $Ca^{2+}$  from sarcoplasmic reticulum.

## Competitive Neuromuscular Blockers (CNMB)

- Structural analogs of Ach, and they act as **antagonists**.
- "**Curare**" is a mixture of naturally occurring alkaloids having neuromuscular blocking activity (Tubocurarine is the most important).
- Others: **mivacurium**, **atracurium**

### Mechanism of action:

- At low doses:
  - They competitively block the Nm → muscle relaxation
  - Their action can be overcome by increasing the concentration of Ach e.g. anticholinesterase (neostigmine)
- At high doses:
  - Block the ion channel at the end plate i.e. can not be reversed by anticholinesterase





### **Effects of CNMB**

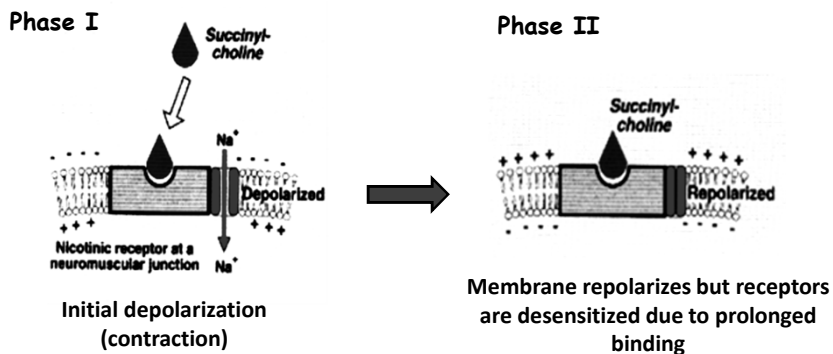
- Not all muscles are equally sensitive to NMB so paralysis occurs in the following sequence:
  - Eye Muscles (double vision)
  - Face Small muscles
  - Pharynx (difficulty in swallowing)
  - Limbs, neck and trunk.
  - Respiratory Muscles (the last one).
- Some CNMB (tubocurarine, mivacurium, and atracurium) may release histamine → ↓BP , flushing, and bronchoconstriction.

### **Drug Interactions**

1. Cholinesterase inhibitors  
e.g. neostigmine → Antagonism
2. Halogenated hydrocarbon anesthetics  
e.g. halothane → Synergism
3. Aminoglycosides antibiotics  
e.g. gentamycin or tobramycin → Synergism
4. Calcium channel blockers:  
Enhancement

## Depolarizing Neuromuscular Blockers (DNMB)

- They are biquaternary ammonium compounds e.g. **decamethonium** & **suxamethonium**
- **Suxamethonium** (succinylcholine) consists of two Ach molecules linked by their acetyl groups, so its action is shorter than decamethonium because it is quickly hydrolyzed by plasma cholinesterase.



### Actions of DNMB

- They produce initial short-lasting muscle fasciculation (contraction), followed by paralysis.
- The sequence of paralysis may be slightly different, but as with CNMB, the respiratory muscles are paralyzed last.
- They have weak histamine releasing action.

### Therapeutic uses of CNMB

- Because of its rapid onset and short duration of action, succinylcholine is useful when rapid endotracheal intubation is required.

### **Adverse effects of DNMB**

- **Malignant Hyperthermia:** Caused by **succinylcholine** and **halothane** is used as an anesthetic. This is treated by rapidly cooling the patient and by administration of **dantrolene**, which blocks release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum  $\rightarrow$   $\downarrow$  heat production & relaxing muscle tone.
- **Apnea and prolonged paralysis:** in patient with genetic deficiency of plasma cholinesterase (apnea due to paralysis of the diaphragm). It can be treated by blood transfusion which contains pseudocholine esterase enzyme.
- **Hyperkalemia:** Succinylcholine increases potassium release from intracellular stores.